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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,723	11/19/2001	Avi J. Ashkenazi	P2730P1C62	9893

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	
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10/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/989,723	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,129-131 and 135-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,129-131 and 135-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The *Remarks/Arguments*, submitted 13 July 2007, has been received and considered.

Claims 124, 129-131 and 135-145 are pending and being examined in the current Office Action.

New/Maintained Rejections

Claim Rejections-35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124, 129-131 and 135-145 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 124, 129-131 and 135-145 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the examiner no longer asserts that **mRNA levels** are not predictive of polypeptide levels. Therefore, the

following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., Nagaraja et al., Waghray et al., Sagnaliev et al., Lilley et al., Wildsmith et al., King et al., Bork et al., Celis et al., and Madoz-Gurpide et al. The following references cited and discussed by Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, Meric et al., Zhigang et al., Wang et al., Munaut et al. The basis of the maintained rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to the isolated nucleic acid of SEQ ID NO: 348, vectors and host cells comprising SEQ ID NO: 348, the full-length coding sequence of the cDNA deposited under ATCC accession number 203044, and fragments of at least 20 bases, wherein the nucleic acid is amplified in lung cell and colon carcinomas. It is noted that the claims do not require that the claimed nucleic acids and encoded polypeptides be overexpressed in any tumor, or have any biological activity. Applicants have gone on the record as relying upon the gene amplification assay as providing utility and enablement for the claimed nucleic acids. See, for example, the Appeal Brief (received 30 August 2005), p. 3.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding the PRO1097 polypeptide had a ΔCt value of at least 1.0 for two out of fourteen lung tumor samples and three of the eight colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170

asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

Firstly, there are several problems with the data provided in this example. Only two out of the fourteen lung cancer samples and three of the eight colon tumor samples tested positive. Therefore, if a sample were taken from an individual with a diagnosis of lung cancer or colon cancer, ***it is more likely than not that this assay would yield a false negative result.*** Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12, especially p. 4, Figure 4) who teach that damaged, precancerous lung epithelium is often aneuploid. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium or between colon tumor samples and normal colon tissue and does not correct for aneuploidy. Thus it is not clear that PRO1097 is amplified

in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium or in cancerous colon tissue versus normal colon tissue. One skilled in the art would not conclude that PRO1097 is a diagnostic probe for lung or colon cancer unless it is clear that PRO1097 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium and in colon tumor tissue relative to normal colon tissue.

Secondly, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of tumor samples had tested positive, the data say nothing about the function of the PRO1097 gene, nor its relationship to mRNA or the PRO1097 polypeptides. The general concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88, of record). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Thus, a gene that is amplified to some extent may have no function in terms of cancer diagnosis or treatment. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33): 21161-21168, of record) speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. *Although gene* ***amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in*** *which they are amplified.*" (emphasis added). The protein encoded by the DDX gene *had been*

characterized as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." There is no evidence in the instant application that PRO1097 confers any growth advantage to a cell; thus, it cannot be presumed that the protein is overexpressed just because the genomic DNA is amplified.

An additional reference that provides evidence that gene amplification does not generally imply a function in the cell is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635, of record). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: ***"In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels,*** implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the*

development of lung adenocarcinoma." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO1097.

The data do not support the specification's assertion that PRO1097 can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1097 gene is amplified in any cancer to the extent that the nucleic acids could be used as cancer diagnostic agents. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are properly maintained.

The only evidence directly related to the possible function of PRO1097 is found in Example 170 of the specification, which indicates that the PRO1097 gene is amplified in two out of fourteen lung tumors and two out of eight colon tumors as compared to a pooled blood DNA sample. The PRO1097 gene was **not** amplified in twelve out of fourteen lung tumor samples and

five out of eight colon tumor samples, thus establishing that it is more likely than not that a lung or colon sample from a patient suspected of having lung or colon cancer will yield a false negative result in the disclosed assay. While it is true that markers for rare cancers are valuable, they are only valuable if the rare tumor is adequately described and distinguished from other tumors.

35 U.S.C. § 112, First Paragraph, Written Description

Claims 139-145 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 2-4 of the previous Office Action (17 April 2007).

Claim limitations are presented to nucleic acids that hybridize to SEQ ID NO: 348 under stringent conditions, as well as host cells and vectors comprising. Applicants discussed amending the independent claim to specify that the isolated nucleic acid "is suitable for *PCR* use" (13 July 2007, p. 5), but did not actually make the amendment.

The specification teaches a polynucleotide (SEQ ID NO: 348). However, the specification does not teach functional or structural characteristics of all claimed polynucleotides. The description of one polynucleotide encoding a PRO polypeptide (SEQ ID NO: 348) is not adequate written description of an entire genus of polynucleotides.

To provide evidence of possession of a claimed genus, the specification must provide

sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of hybridization stringency. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequence of SEQ ID NO: 348 referred to above, the skilled artisan cannot envision the detailed chemical structure of all claimed polynucleotides and all encompassed PRO polynucleotides, and therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The nucleotide *itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 348, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants have referred to the Written Description Guidelines, especially Example 9, issued by the U.S. Patent Office to argue that they are in possession of the genus of nucleic acids that hybridize to SEQ ID NO: 348. However, the claims of the instant application and the facts laid out in Example 9 differ substantially. Firstly, that example makes use of highly stringent conditions, defined as 6X SSC and 65 degrees Celsius. The instant claims do not recite 6X SSC and 65 degrees Celsius, but rather more moderate hybridization stringency conditions. Thus, a large number of nucleic acids will hybridize to SEQ ID NO: 348 under the conditions specified in the claims.

Secondly, Claim 1 in the Example recites a required function for the nucleic acids that hybridize to the claimed nucleic acids, thus further limiting the genus. In fact, the nucleic acids found to hybridize in the Example were expressed and tested for activity. The instant claims have no such requirement for a required function, and there was no reduction to practice to determine

functions for the hybridizing nucleic acids.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 139-145 under 35 U.S.C. 112, second paragraph, for being indefinite is *maintained.*

As discussed in the previous Office Action, claims 139-145 are rendered indefinite because of the phrase "is suitable for use as a PCR primer or probe." Applicants neither defined nor removed the phrase. It should be noted that the examiner did *not* suggest adding "is suitable for PCR use," but instead suggested removing the phrase (17 April 2007, p. 5).

Conclusion

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

SLW
22 September 2007

Eileen B. O'Hara
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PRIMARY EXAMINER